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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,419	07/24/2000	MAX F. ROTHSCHILD	P03815US1	2593

22885 7590 07/16/2003

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EXAMINER

SWITZER, JULIET CAROLINE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/380,419	<b>Applicant(s)</b> ROTHSCHILD ET AL.	
	<b>Examiner</b> Juliet C. Switzer	<b>Art Unit</b> 1634	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 February 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-11, 20-23, 29, 30 and 32-36 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11, 20-23, 29, 30 and 32-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 May 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

1. Applicant's submission filed on 2/21/03 has been entered. Claims 1, 2, 4-6, 20, 22, 29, and 30 have been amended, claims 34-36 have been added, and claims 12, 28, and 31 have been cancelled. Claims 1-11, 20-23, and 29-30, 32-36 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. The formal drawings have been received and are approved by the examiner.
3. It is noted that there is a discrepancy between the clean copy of the claims and the marked up copy of the claims. Namely, the clean copy of the claims adds new claims 34, 35, and 36, while the marked up copy includes an additional claim 37. Since the clean copy of the claims is the official copy of the claims, the official claim set includes new claims 34, 35, and 36, and NOT claim 37.

### ***Sequence Rules***

4. The paper copy of the Sequence Listing, the CRF, and amendments to the specification have all been received and entered. Prior to entry of the CRF, the STIC modified the file by deleting non-ASCII "garbage" from the end of the file.
5. The application is in compliance with the sequence rules.

### ***Claim Rejections - 35 USC § 112***

6. Claims 1-2, 4-11, 20-23, 29-30, and 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying a pig

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which possesses a genotype indicative of the pig having less back fat than pigs with a different genotype, indicative of the pig having a lower daily gain than pigs with a different genotype, or of pigs having a lower feed intake than a pig with a different genotype, wherein said method comprises screening DNA of the pig for a G → A point mutation at position 678 of SEQ ID NO: 1 (of the sequence listing) and wherein the absence of the mutation is indicative of a pig having the recited traits, does not reasonably provide enablement for methods which screen other animals or methods which utilize other polymorphisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The prior art teaches one polymorphism in humans which is associated with obesity (Yeo *et al.* 1998. *Nature Genetics*, Vol. 20, p. 111-112). Methods for screening humans using this polymorphism are also enabled. In addition, claims 28 and 31 have been amended so that they encompass screening methods using any gene, any polymorphism and any animal. These claims are included in this rejection insofar as they would pertain to screening of the MC4R gene.

Each of the rejected claims are broadly drawn to include at least one of the following: methods for screening any animal or methods for screening which utilize a polymorphism not limited to the single disclosed polymorphism in this application (i.e. the G → A point mutation at position 678 of SEQ ID NO: 1).

The specification provides a single working example which demonstrates that pigs homozygous for an G at position 678 of SEQ ID NO: 1 have less backfat, lower daily gain, and lower feed intake than pigs homozygous for an A at position 678. The prior art is silent with respect to other possible polymorphisms in the MC4R gene or with respect to the association of

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this particular polymorphism with any metabolic trait in any other animal. Neither the specification nor the prior art provide evidence of any universal correlation between polymorphisms in MC4R and metabolic traits which would conclusively associate the polymorphism instantly disclosed with metabolic traits in any other animal.

The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. The amount of direction or guidance presented in the specification and the prior art of only one point mutation in the MC4R gene of one species of animal is minimal, given that just the redundancy of the genetic code would allow for several thousand different sequences when conserved or non-conserved mutations are considered, millions of different sequences for the pig MC4R gene may exist which may, or may not, have substantial functional differences or association with the traits of interest herein. There are no working examples of additional sequences other than those disclosed in either the specification or the prior art.

Furthermore, there is no evidence in the specification provided that the identified polymorphism is causative of the observed traits. This is a significant absence of evidence, since it is possible that the polymorphism is merely a marker for the causative genotype. In light of the fact that the causative genotype has not been identified, it is unpredictable as to whether or not markers which are linked to the instantly disclosed polymorphism would be informative for the traits of interest herein (for example, as claimed in claims 29 and 30).

Although the level of skill in the art of nucleic acid analysis is high (the Ph.D. degree with laboratory experience), the quantity of experimentation that would be necessary to determine even one additional polymorphism in the pig MC4R gene is substantial since there is

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no predictability for which sequences exist which code for polymorphisms in pig MC4R genes. Applicants have not disclosed how one would go about detecting additional polymorphisms associated with the traits of interest herein. Because there is no reason to expect that any additional polymorphism is associated with the instantly discussed metabolic traits and because of the very large number of possible polymorphisms, screening for additional polymorphisms that would be indicators of these traits would require the rearing and subsequent slaughtering of many, many pigs in order to analyze their metabolic traits and in order to screen the MC4R gene for informative polymorphisms. There is no evidence, however, of any frequency of significant polymorphisms. Further, even if polymorphisms were detected, the polymorphism may not correlate to polymorphic traits. The instantly disclosed polymorphism may be coincident with and unrelated to a different, unlinked (on the chromosome) polymorphism such as another MC4R polymorphism or a polymorphism in an undetermined gene that actually determines the metabolic traits. The instantly disclosed polymorphism would not have any meaning or effect, but might appear to influence metabolic traits due to its close proximity to some other gene.

Furthermore, the level of unpredictability and the level of experimentation required to expand the instantly disclosed methods to include animals of other species are also quite high. There is no teaching in the specification that the disclosed polymorphism even exists in animals of other species. Since there is not evidence that the disclosed polymorphism is causative of the traits (as discussed above), it is highly unpredictable as to whether the polymorphism would mark the same traits in other animals. Further, in order to provide such evidence the skilled artisan would be required to undertake extensive studies of the metabolic traits of hundreds upon

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hundreds of different individual animals of each of many different species of animal. Such experimentation would be inventive in itself.

Due to the broad nature of the claims, the presence of only one working example, the extreme unpredictability of polymorphisms in the art, combined with the absence of teaching in the prior and the large quantity of experimentation necessary in the art support a conclusion that undue experimentation is required to make and use the invention as broadly claimed.

7. Claims 1-11, 20-23, 29, 30, and 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is not clear how the method steps of the claim accomplish the goal of the method as set forth by the preamble. Applicant has clarified the goal of the method to recite a "method for identifying an animal which possesses a genotype associated with one or more favorable metabolic traits...", however the method steps are directed towards detecting a polymorphism. The method steps of claim 1 do not set forth particularly and distinctly how the identification of animals recited in the preamble is to take place, or that it does take place. Therefore, it is not clear if the method is intended to be a method for identifying an animal or a method for detecting a polymorphism. Claims which depend from claim 1 are indefinite for this reason as well.

In claim 5 the phrase "the marker" lacks proper antecedent basis in the claims because the claim does not previously recite a marker.

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Claims 20-23 are indefinite for failing to recite a final process step which agrees back with the preamble. Claims 20-23 are drawn to a method of identifying an animal which possesses a genotype associated with variation in one or more metabolic traits. The final process step of the claims recites “wherein the presence of a TaqI restriction pattern identifies the presence of a polymorphic site in the MC4R gene...” but the claim does not make the connection between the genotype associated with a metabolic trait and the presence of the TaqI restriction site. That is, the method steps of the claim designate how to know if there is a polymorphic site “associated with variation” present, but it does not instruct how to identify an animal with a genotype associated with variation. Claim 20 does not set forth any specific desired genotypes or how these are identified. Furthermore, the claims are indefinite because the purpose of the method as set forth in the preamble is unclear. The preamble indicates that the method is for identifying an animal which possesses a genotype associated with variation in one or more metabolic traits. This is unclear, because any animal, at least any pig with a MC4R gene would have a genotype that is associated with variation in one or more of the listed traits. Claim 1 does not specify that animals possessing genotypes indicative of particular traits are identified, merely that animals possessing genotypes associated with variation are identified. Thus, the claim remains unclear.

In claim 21, the phrase “the desired genotype” lacks proper antecedent basis because the claims do not previously set forth a desired genotype.

Claim 22 is indefinite over the recitation of “at base 678 of the amplified product” because claim 21 recites two amplified products and it is not clear which amplified product the claim intends. Furthermore, the claim is indefinite over the recitation “when a restriction enzyme which cuts at the same recognition site as Taq I is used” because it is not clear when the



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restriction enzyme is used or what it is used to digest. That is, is the restriction enzyme the same one that is recited in line 8 of claim 21 (and thus is Taq I) or is being used at some other time?

In claim 29, the phrase "the DNA marker known to be associated" lacks proper antecedent basis in the claim as the claim does not previously recite such a marker.

Claims 34-36 are indefinite because the recited primer pairs will not produce a PCR sequence that has a polymorphic site at position 678 of the amplification product, thus it is not clear how one can practice the method of claim 2 which requires detecting a polymorphic site at position 678 of the PCR sequence. It appears that the amplification products produced using the recited primer pairs produce a product that is different from SEQ ID NO: 1, yet these claims depend from claims 2 and 1 which require detecting a polymorphism at position 678 of SEQ ID NO: 1, and detecting the polymorphism at position 678 of a PCR sequence.

#### ***New Matter Rejection***

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "the linked marker known to be associated with a metabolic trait" in claim 29 appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. The specification does not provide written description

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to support the recitation that markers S0441, GHT0433, and S0313 are known to be associated with any metabolic trait. The specification teaches only that these markers are linked to the MC4R gene (see p. 9, line 5). Since no basis has been identified, the claims are rejected as incorporating new matter.

**Response to Remarks**

Applicants argue that they have shown that polymorphism in the MC4R gene has been located and is associated with the metabolic traits of fat content, growth rate, and feed consumption in animals. However, as pointed out in the rejections of record, this correlation has only been shown for pigs, not for all animals. Thus, this statement is correct in that pigs are animals, but it is not true to say that applicant has shown this correlation for all animals. Applicants point out that this particular polymorphism is within a highly conserved region among melanocortin receptors and that they have provided an alignment of the predicted amino acid sequences of the pig MC4R with the MC4R protein from other species, demonstrating that the aspartic acid found at position 298 of the seventh transmembrane domain is very highly conserved in the MC4R protein among species. The fact that the MC4R protein is conserved among species is not sufficient to establish that this polymorphism exists in other species because there is no correlation between this conservation of sequence and the conservation of polymorphism among species. That is, there is no reason to believe that this same polymorphism would exist in other species, and no evidence has been provided that would support this assertion. The appearance of polymorphism among different species is highly unpredictable, as

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discussed in the rejection, and that the protein is conserved among species is not evidence that polymorphic events are also conserved among species.

Furthermore, it is noted that the examiner's comments with regard to unpredictability are focused on the fact that it is highly unpredictable as to whether or not any other polymorphisms exist in the porcine MC4R gene OR whether or not the instant polymorphism exists in other species of animals which have a MC4R gene. Although it may be routine experimentation to search for such polymorphisms, this does not subtract from the fact that they actually may not exist. The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. First, it is unpredictable whether any additional polymorphisms exist in the porcine MC4R gene, or whether the instantly disclosed polymorphism is present in the genomes of other animals. Genetic polymorphisms are the elements which render individuals unique, but many genes are highly conserved and do not yield polymorphisms between individuals of a single species. Some genes even lack polymorphisms between members of different species. The specification and prior art provide no guidance as to whether any other polymorphisms exist, or whether the instantly disclosed polymorphism is present in the genomes of other animals besides pigs. Second, after a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with favorable meat quality. Thus, the claimed method of screening animals, for enablement of the full scope, requires the use of unpredictable and potentially non-existent products. As noted in *In re Vaeck*, 20 USPQ2d 1438 (CA FC 1991) regarding enablement, "This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

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Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. See Fisher, 427 F.2d at 839, 166 USPQ at 24." In this case, the genus is itself undefined and undue experimentation is required to identify which polymorphisms, none of which are known other than the disclosed example, have the utility of being associated with metabolic traits in animals.

Thus, the rejection is maintained.

Amendment of claim 1 obviated the rejections against claim 1 in part, but new rejections are set forth in light of the amended claim.

Amendment of claim 2 overcame the rejection of claim 2, 4, 5, and 6. Amendment of claim 4 overcame the rejection claim 4 with regard to what is associated with variation in fat content.

Applicant asserts that claim 20 has been amended to recite a final process step that meets the preamble, however the examiner does not agree, for the reasons stated in the modified rejection based on the new claim language. Further clarification of these claims is required.

New 112 2<sup>nd</sup> rejections were made to address the amendments to the claims. In addition, a 112 1<sup>st</sup> paragraph, New Matter rejection was set forth.

### ***Conclusion***

8. No claims are allowed. However, claim 3 is free of all 112 1<sup>st</sup> paragraph rejections and would be allowable if written in independent form, overcoming all 112 2<sup>nd</sup> rejections and including all of the limitations set forth in the claim as currently pending.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Juliet C Switzer  
Examiner  
Art Unit 1634

July 2, 2003



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